

Fully Polarizable QM/MM Calculations: An Application to the Nonbonded Iodine–Oxygen Interaction in Dimethyl-2-Iodobenzoylphosphonate

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ABSTRACT: The compound dimethyl-2-iodobenzoylphosphonate is unusual in that it forms well-ordered crystals that clearly show short iodine-oxygen interactions in which both the iodine and the oxygen are in their normal oxidation states. These interactions were studied using a new hybrid quantum mechanical–molecular mechanical approach that employs a polarizable molecular mechanics component. The electric field at the molecular mechanics atoms was calculated from a distributed multipole expansion of the wave function; this induced dipoles on the molecular mechanics atoms. The electrostatic potential in a spherical shell around the induced dipoles was reproduced through induced charges on the atomic center and those bonded to it using an analytical (rather than numerical) procedure. The new atomic charges (induced charges plus permanent charges) were then able to interact with the quantum mechanical entity and polarize the wave function. The procedure was iterated to convergence. The calculations show that the iodine atom becomes

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more positive in the crystal environment (modeled by a chain of three molecules of dimethyl-2-iodobenzoylphosphonate). Thus, while the cooperative effects of the crystal environment may not be the only feature stabilizing this unusual interaction, they do play a significant role in reducing the otherwise unfavourable iodine–oxygen monopole–monopole interaction. © 2000 John Wiley & Sons, Inc. J Comput Chem 21: 478–482, 2000

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Introduction

The compound dimethyl-2-iodobenzoylphosphonate (Fig. 1) is unusual in that it forms well-ordered crystals that clearly show short iodine–oxygen interactions in which both the iodine and the oxygen are in their normal oxidation states.¹ The cooperative effects that stabilize this interaction have been studied using hybrid quantum mechanical molecular mechanical (QM/MM) calculations that employ a new approach to polarizing the molecular mechanics component.

Nonbonded interactions between iodine atoms and neighboring atoms of high electronegativity (N, O, F) have been found at distances much shorter than the expected van der Waals' separation (3.5 Å for I...O).^{1–3} (Here the analysis applies to iodine atoms in their normal oxidation state and covalently bonded to carbon.) The I...O distances may be as short as 2.9 Å, and while

most authors do not explicitly mention this interaction, it is of considerable interest to speculate whether this represents a secondary bonding interaction and what its origin might be. Previous suggestions include the iodine equivalent of a hydrogen bond,⁴ coordination into iodine 5d-orbitals,² the halogen polarizability,⁵ and electrostatic interactions with the iodine quadrupole.⁶ Such I...O interactions have been implicated in the binding of biologically important molecules.^{2,3} In dimethyl-2-iodobenzoylphosphonate, there is an intramolecular I...O distance of 3.1 Å (to the neighboring C=O group) and an intermolecular one of 3.0 Å (to the P=O group of a translationally related molecule). The molecules thus form chains linked by the C—I...O=P interactions. To determine the effect of the crystal environment on the I...O interaction, we have carried out a theoretical investigation on the isolated and three translationally linked molecules. In particular, both the iodine and oxygen electronegativities should give rise to a repulsive electrostatic interaction, and so we have investigated the extent

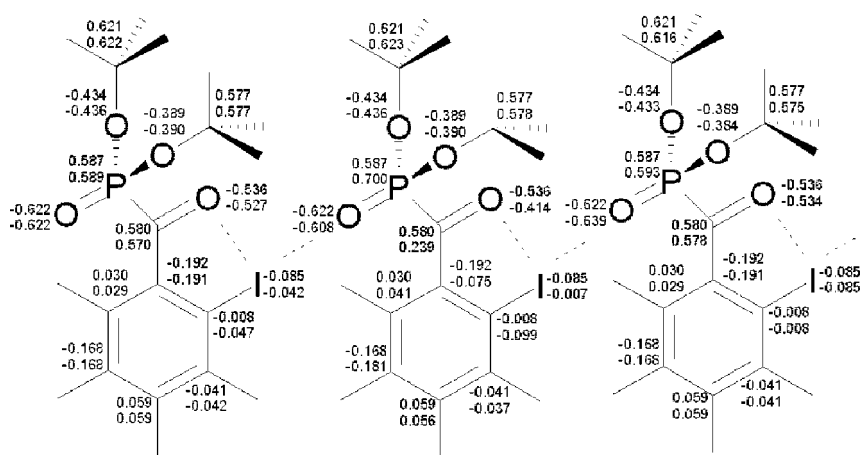


FIGURE 1. Three adjacent molecules of 2-iodobenzoylphosphonate in the arrangement used in the calculations. The short iodine–oxygen contacts are indicated by dashed lines. The BLYP density functional monomer charges (top) and the QM(BLYP)/MM(pol) hybrid charges (bottom) are shown for the heavy atoms. For the central monomer, the hybrid charges are quantum mechanical, for the left and right monomers, the hybrid charges are polarizable molecular mechanics charges. The H-atoms are shown but not labeled.

to which the iodine atomic charges are modified by the immediate crystal environment (modeled by two flanking molecules, as shown in Fig. 1).

Methods

The two most popular types of computed atomic charges—Mulliken charges and molecular electrostatic potential-derived charges—each have their limitations. The former type is excellent for qualitative studies, but fails to give a good quantitative description of electrostatic properties such as dipoles; the latter type is ideal for quantitative studies, but may fail in qualitative studies involving buried atoms.⁷ In calculations on our trimer, basis set superposition effects⁸ are likely to be significant because the size of the systems precludes the use of very large basis sets. Consequently, we have used two novel approaches to study this problem. The first approach entailed the use of the *multifit* code⁹ to derive multipole-derived charges. Here, the potential due to an accurate atom-based multipole expansion¹⁰ of the wave function is reproduced by the best set of charges on the atom and those bonded to it.^{7,11} Because multipole-derived charges retain the link between the charge on an atom and the potential due to the basis functions on that atom they are useful for both qualitative and quantitative studies.⁷ The second approach involved hybrid QM/MM calculations on the trimer. Hybrid QM/MM calculations do not suffer from basis set superposition effects,¹² and so the charges on atoms at the interface will not be erroneously polarized. However, hybrid QM/MM approaches do not usually include polarization of the molecular mechanics entity. To aid our interpretation we have, therefore, included induction effects in the MM entity by modifying the traditional method of induced dipoles. Here, the induced dipoles are converted into induced charges on the atom and those bonded to it. Again, this was done using the *multifit* code⁹ used to derive the atomic charges. The method is illustrated in Figure 2, and its ability to describe induction effects in purely classical systems is described elsewhere.¹³ There have been other approaches to polarization of the molecular mechanics entity in hybrid calculations,¹⁴ for example, based on the fluctuating charge method.¹⁵ One advantage of the method proposed here is that the induced charges are treated on a similar footing to the purely quantum mechanical charges.

The calculations were carried out on a monomeric and a trimeric unit extracted using sym-

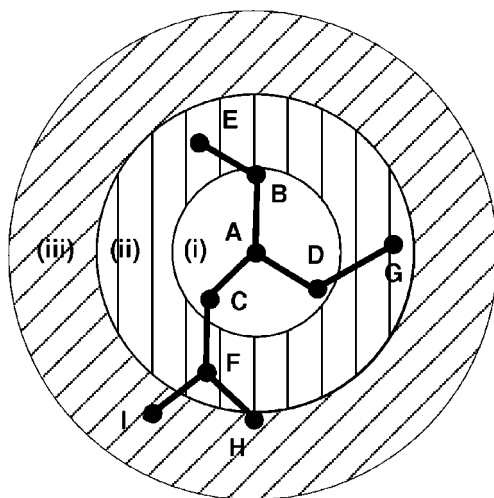


FIGURE 2. The scheme for obtaining induced charges from induced dipoles. The fitting is carried out analytically, and so does not require a numerical grid. The induced charges in zone (i) at atoms A, B, C, and D reproduce the electrostatic potential due to the induced dipole at A throughout the outer spherical region (iii). The same method is used to reproduce the effects of a multipole series at A by atomic charges at atoms A, B, C, and D.

metry from the crystallographic coordinates¹ (see Fig. 1). The wave functions for the monomer and trimer were determined using nonlocal density functional calculations, as implemented in the CADPAC 6.1 and GAUSSIAN 98 software,¹⁶ with a DZVP double-zeta plus polarization basis set.¹⁷ The Becke 88 functional was used for exchange,¹⁸ and the Lee–Yang–Parr functional was used for correlation¹⁹ (together denoted BLYP).

In the hybrid calculations, only the central molecule was treated quantum mechanically while the other two molecules were treated classically as a set of point charges and isotropic polarizabilities,²⁰ α . The two classical molecules were able to polarize the wave function through the 1-electron Hamiltonian. The field, E , at the molecular mechanics atoms was evaluated from a distributed multipole expansion of the wave function (up to rank 5) and converted into induced dipoles, μ , using the usual equation $\mu = \alpha E$. These induced dipoles were then converted into “induced charges” using the procedure described above, and so both the quantum and the classical molecules were polarized. The initial monomer charges were then modified by adding the new induced charges. The procedure was iterated until the charges converged, which occurred after four cycles, and the results are shown in Figure 1.

Results and Discussion

Analysis of the hybrid QM/MM results show that the iodine atoms become more positive when they interact in the trimer. Thus for the polarisable molecular mechanics entity (left monomer in Fig. 1) the iodine charge increases from -0.085 to -0.042 , while for the quantum mechanics entity (central monomer in Fig. 1) the charge increases from -0.085 to -0.007 . Here, the change is not identical, (a) because the environment is different, and (b) because we have not optimized the polarizabilities. Nevertheless, we can conclude that polarization effects within the crystal environment result in a more positive iodine atom, and hence, a reduction in unfavorable repulsion effects. (Similar results were obtained with hybrid Hartree–Fock QM/MM calculations, results not shown.) The noninteracting iodine in the right-hand molecule has essentially the same charge as the monomer. In the density functional and Hartree–Fock calculations on the trimer there is a small net flow of charge from the right molecule to the left (results not shown). This charge flow implies that the wave function may be subject to basis set superposition effects. Nevertheless, the same effect is seen, namely that interacting iodine atoms become more positive in the trimer. By comparison, the percentage change in the oxygen charge is much smaller, so the effect on the crystal stability is much less. Thus, our calculations suggest a variation on the donor–acceptor explanation:^{4,21} electron acceptors are a general feature of crystal structures containing short I...O interactions, but their role in the crystal environment may be to redistribute the charge, thereby permitting the iodine to become more positive.

To conclude, we suggest that the iodine atoms in dimethyl-2-iodobenzoylphosphonate becomes more positive through the cooperative effects that occur upon crystallization. This alone is not sufficient to explain why I...O nonbonded interactions are so short or why C—I...O interactions are generally linear.³ Nevertheless, these polarizing cooperative effects may contribute significantly to the stability of the crystals. The hybrid QM/MM calculations used in this work included a polarizable molecular mechanics entity, and so the method may have other applications, for example, in the study of enzyme mechanisms. Interestingly, the fluoro-, chloro-, and bromo-ketophosphonates form oils that cannot be crystallized. Molecules such as dimethyl-2-iodobenzoylphosphonate, in which the stability is increased through subtle polarizing effects, may

form useful components in molecular electronic devices.

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Supplementary Material

Density functional and Hartree–Fock multfit and Mulliken charges for the monomer, trimer, and hybrid system plus coordinates and isotropic polarizabilities for dimethyl 2-iodobenzoylphosphonate and 40 references to articles containing crystal structures with short I...O intermolecular interactions (three pages); see any current masthead for ordering information and for Web access instructions.

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